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ORIGINAL CONTRIBUTION

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A prospective, open-label, multicentric, single-arm, post-marketing clinical study to evaluate effectiveness and safety of Cross-Linked Sodium Hyaluronate 24mg with Lidocaine 3mg Injection in subjects undergoing treatment for facial wrinkles and lip augmentation

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Abstract

Background: Hyaluronic acid (HA) fillers are quite commonly used since several years for soft tissue augmentation.

Aim: The purpose of this study was to evaluate primarily the safety and secondarily the clinical effectiveness of Cross-Linked Sodium Hyaluronate 24 mg with Lidocaine 3 mg (Jeunesso 24L) injection, in subjects undergoing treatment for facial wrinkles and lip augmentation.

Method: Patients between the age groups of 18 and 75 years, who were seeking soft tissue augmentation treatment on the face and with wrinkle severity score (WSS) ≥2 for bilateral Nasolabial Folds (NLF), were included in the study. The appropriate quantity of the filler was injected at the treatment site. Clinical efficacy assessments were conducted independently at 3 and 6 months after baseline. Clinical efficacy was assessed using Wrinkle Severity Rating Scale (WSRS) and a Global Aesthetic Improvement Scale (GAIS).

Results: The mean pain score was found to be 2.57 ± 2.06 immediately after injection which was reduced to 0.1 ± 0.675 at 15 min and this further subsided to "No Pain" in any of the participants at 60 min post the injection. WSRS mean score before treatment was 2.76, which were significantly reduced to 2.14, at 3 months. Majority of participants found an improvement in the marionette line severity. Also, significant improvements were seen in the perioral and lip areas. The Study filler was well-tolerated and no side effects were reported.

Conclusion: The study indicates that this particular filler, HA+L, is useful for cosmetic improvements in the nasolabial folds and for enhancement of the lips.

KEYWORDS
aging treatment, Cross-Linked Sodium Hyaluronate, facial wrinkles, lip augmentation

1 | INTRODUCTION

Factors like smoking, genetics, sun exposure, and muscle activity contribute to external signs of aging in people.[1,2] This can lead to reduced collagen production, which is the main protein that supports the skin and its flexibility. Causes for structural facial aging can be attributed to skeletal resorption, volumetric fat depletion, redistribution of skin, and soft tissue.[3] With aging, the skeleton and the facial tissues shrink, leading to features like droopy eyes and tear trough deformity. The skin also loses its suppleness, due to diminished sebaceous gland activity.[4]

Various invasive and non-invasive treatment options are available for reducing the signs of aging.[5] For longer than half a century, the idea of non-invasive treatments replacing a doctor's scalpel has piqued interest in medicine.[6] Chemical peeling, laser resurfacing, and dermabrasion can treat superficial wrinkles. However, for deeper wrinkles, injectable derma fillers, facial surgery, and botulinum toxin treatments are required.

It is crucial to realize that volume loss is the most important feature of facial aging, and that replacing this volume with fillers (non-surgical therapeutic algorithm) is the most critical factor in facial rejuvenation.[7]

Injectable dermal fillers are a non-surgical treatment which can reduce facial wrinkles, folds, and lines by restoring facial volume. This helps in combating visible signs of aging by rejuvenating the skin. Injectable dermal fillers are less time consuming, cause less morbidity and provide an immediate benefit, which allows the individual to return to their routine immediately after the treatment.[4]

Also, for acne scar treatment, subcision followed by dermal fillers gives better result in comparison with single modality treatments used for the acne scars. Fillers injection in scars leads to formation of collagen ensuing soft-tissue augmentation.[8]

Most temporary dermal fillers, containing both natural and synthetic materials, are usually safe and effective. However, animal protein used in some dermal fillers increases risks of allergic reactions. Hyaluronic acid (HA) is a naturally occurring linear polysaccharide with an uniform structure in all living organisms. It promotes moisture by allowing the water molecules to attach to it, acting as a lubricant for skin, bones, eyes, and joints in animals. Commercially, it is produced commonly from bacterial sources rather than animal or human sources and thus, allergic reactions associated with HA are rare.[9–11]

Hyaluronic acid fillers are one of the most frequently used agents for soft tissue augmentation, due to its tolerability and long-lasting effects. An advantage of HA includes the reversibility of the treatment through hyaluronidase injection, which is more convenient than surgery and grants the procedure predictability in the results. Lidocaine (L) is a very commonly used local anesthetic, which can be combined with dermal fillers, to reduce the pain caused by the treatment procedure.

HA+L is a clear transparent gel made of novel cross-linked hyaluronic acid of injectable grade, formulated with hyaluronic acid from bio-fermentation origin. HA+L is available in single-use glass syringes, prefilled with 1ml sterile cross-linked hyaluronic acid gel.

Advanced cohesive 3D matrix-based gel formulation resists degradation for an extended duration, has uniform consistency and flows evenly. This makes it suitable for injecting into deep skin depressions. This treatment can also be useful for lip definition and enhancement of lips. The gel also consists of 0.3% lidocaine for reduction of treatment pain and increased patient comfort.[13]

The purpose of this study was to evaluate primarily the safety and secondarily the clinical effectiveness of Cross-Linked Sodium Hyaluronate 24 mg with Lidocaine 3 mg (Jeunesso 24L) Injection in subjects undergoing treatment for facial wrinkles and lip augmentation. This is a post-marketing, multicentric, open-label, clinical trial to check the injection comfort and the ease of injections.

2 | METHODOLOGY

2.1 | Study design

The study was a phase IV, single arm, single-blind, clinical study conducted at three hospitals in the cities of India, located at Mumbai, Hyderabad, and Bangalore. Institutional ethics committee of each of the sites approved the study protocol and the related documents before initiating the clinical trials.

TABLE 1 The wrinkle severity rating scale

Score	Description
5	Extreme: Extremely deep and long folds, detrimental to facial appearance; 2–4-mm visible V-shaped fold when stretched; unlikely to have satisfactory correction with injectable implant alone
4	Severe: Very long and deep folds; prominent facial feature; less than 2-mm visible fold when stretched; significant improvement is expected from injectable implant
3	Moderate: Moderately deep folds; clear facial feature visible at normal appearance but not when stretched; excellent correction is expected from injectable implant
2	Mild: Shallow but visible fold with a slight indentation; minor facial feature; implant is expected to produce a slight improvement in appearance
1	continuous skin line with perceptible wrinkle

2.2 | Inclusion criteria

- Subjects of both genders, aged between 18 and 75 years, willing to participate in the study and ready to comply with the procedures.
- The participants who were seeking soft tissue augmentation treatment on the face; with folds, lines, wrinkles in the malar area, perioral line(s), nasolabial fold(s), marionette lines, and jaw lines.
- Individuals with wrinkle severity score (WSS) ≥2 for bilateral Nasolabial Folds (NLF) were included in the study. (Table 1)

2.3 | Exclusion criteria

- Individuals at risk in terms of precautions, warnings, and contra-indications
- Individuals who underwent previous injections of semi-permanent/ permanent filler in the injected areas
- Pregnant/lactating women
- Participants allergic to treatment products
- Participants who had a chemical peel at the NLF area within 4 weeks prior to study entry.
- Participant treated with Botox® injections in the past.
- Patients who had developed tolerance to antibiotics or corticosteroids, or having personal or family history of hypo-hyper skin pigmentation and related disorders; any unhealed wounds or infection, a known history of keloids or bleeding disorders; active inflammatory process; immune compromised/immune suppressed.
- Patients on medication with blood thinners; severe physical, neurological, or mental conditions.
- Subjects with excessive facial hair which might interfere with the study of the wrinkle assessments were also excluded from the study.

2.4 | Methodology

Initially, 101 subjects were contacted for the study, either from the hospital's databases or from doctor's referral.

Out of this, 94 subjects were enrolled for the study. Prior to conducting any study-specific tests or procedures, the benefits and risks of the study were explained to the participant in given information sheet. All the study participants voluntarily provided a written informed consent before any screening procedures were initiated. This process was conducted according to the Clinical Trial Rules 2019 laid by The Central Drugs Standard Control Organisation (CDSCO), India.

This study was conducted in accordance with ICH-GCP, ISO 14155, Declaration of Helsinki, Medical Device Directives of Global Harmonization Task Force and all the pertinent local regulations. Each enrolled participant received Information Sheet and diary containing details of adverse event and concomitant medication.

TABLE 2 Visual Analog Pain Scale

Grade	Level of pain
0	No Pain
1–3	Mild Pain
4–6	Moderate Pain
7–10	Worst Pain

Baseline characteristics like age, gender, and race were recorded at screening. Fitzpatrick skin photography type was also evaluated and categorized from type I to type VI. History of smoking, alcohol drinking habit, and general medical conditions were recorded before initiation of any study procedure. The participants who had co-existing disease were allowed to continue pre-procedural medication throughout the study period.

2.5 | Injection technique

No-touch technique for treatment injection procedure was followed in the study. HA+L is available in single-use glass prefilled syringes (PFS), with 1ml sterile cross-linked hyaluronic acid gel and includes 2 single-use 27G 1/2 inch sterile needles. The rubber tip cap of the HA+L syringe was opened and the needle firmly attached with the luer lock of the PFS. The injectability of the syringe was checked by pressing plunger rod slightly. Some gel was allowed to come out of the needle to confirm the clarity. The appropriate quantity of device was injected or implanted at the chosen treatment site. The individual investigator with a specific training in similar injection techniques determined the specific treatment area, the volume of the drug at both right and left side, and the depth of the injection.

Topical anesthesia was applied to the treatment sites prior to the injection.

3 | EVALUATION

After completion of the injection procedure, the participants were kept under observation for one hour and the response to injection for pain score was evaluated immediately after injection and every 15 min after the injection till 60 min. Pain at injection site was assessed using the Visual Analogue Scale. Ease of injection was evaluated by the injectors, while participants along with injector assessed the level of injection pain (Table 2).

All participants were asked to come to the clinic for follow-up at Day 90 and 180. Also, they were instructed to visit clinic any time in between, if there was any pain at the site of treatment or any unusual symptoms developed.

The patient and an evaluating investigator independently assessed the efficacy of the treatment at the intervals of three and six months after the baseline. After the end of the treatment, the patient was asked to assess the tolerability by journaling every day for two weeks to record adverse events. The investigator assessed

the severity of adverse events at three and 6 months post-initiation of the treatment.

Wrinkle Severity Rating Scale (WSRS) and Global Aesthetic Improvement Scale (GAIS) were used to test the clinical efficacy of the treatment. Wrinkle Severity Rating Scale (WSRS) is a relative scale, which uses photographs to generate results. The scale is specifically designed to quantify facial folds. The severity of folds is scored on basis of the visual appearance of the length and depth of nasolabial folds, without referencing pre-treatment appearance (Table 1). Global Aesthetic Improvement Scale (GAIS) is an absolute scale in which an investigator compares the patient's appearance during follow-up to a pre-treatment high-magnification photograph and grades improvement in each of the nasolabial folds (Table 3).

At the follow-ups, WSRS and GAIS scores were determined. The former is the primary and the latter is the secondary endpoint.

Photographs of the participant were obtained/ recorded before initiation of the procedure and after completion of 180 days (Figures 1 and 2).

The secondary efficacy endpoints also included perioral and lip area enhancement which was assessed based on 2 parameters: (a) Barcode Lines Assessment (b) Lip Enhancement Score. Barcode lines assessment was done by evaluating severity scored on Lemperle Rating Scale (Table 4). Lip enhancement score was evaluated by the Volume Assessment and Vermillion Border Assessment of lip.[14] (Table 3).

3.1 | Statistical analysis

Data were analyzed using descriptive statistical techniques (i.e., Frequency distribution tables and continuous data by summary statistics were used to present categorical data). Paired *t*-test was used for pain assessments.

4 | RESULTS

Of the 101 participants who were initially screened, 4 subjects refused to undergo the treatment at screening and the complete data of 03 subjects was not available. Thus, a total of 94 participants were enrolled in the study and of this population, 89 participants completed the 6 months of follow-up, whereas 05 participants were lost to follow-up. All participants were of Indian Asian origin. Fitzpatrick skin photograph type was evaluated at baseline, and it was observed that more than 62% of the participants were from Type IV (48.94%). (Table 5) None of the participants had a current history of smoking or alcohol intake. Medical history was reported with 2 participants being diabetic and 1 with mild mental depression and they were continued with their medications during the study.

During the procedure, as per physician, the injection was provided to either right or left side of the face or both the side of the face. The mean injected volume per participant was with a range of 0.05 ml to 2.5 ml on each side of face. Total volume injected was with range of 0.1–5 ml as described in Table 6. The depth of injections was mostly intradermal, mid to deep dermal, sub-dermal, submucosal, or supra-periosteal layer. Deep injections with coning were the most commonly used injection method along with linear, cross-threading, fern-like, or fanning techniques. Injection technique of more than one type was used in all patients.

4.1 | Efficacy and safety

4.1.1 | Pain assessment

The pain score observed were in the range of scale of minimum Zero (0) to maximum of Eight (8). Immediately after injection, 75% participant showed mild to moderate pain and only 1 participant showed worse pain. After 15 min of injection, 95% participants had no pain. While at 30 min, only 2 participants and at 45 min, only 1 participant had mild pain and this completely subsided in all patients at 60 min post-injection. These improvements in pain intensity were observed in participants with injection either on the right side or on the left side of the face. The mean pain score was found to be 2.57 ± 2.06 immediately after injection which was reduced to 0.1 ± 0.675 at 15 min and this further subsided to "No Pain" in any of the participants at 60 min post the injections.

4.1.2 | Nasolabial fold

The evaluating investigator rated the nasolabial folds at base-level and at three and 6 months after the treatment. HA+L treatment showed

TABLE 3 The global aesthetic improvement scale.

Rating	Description
Very much improved	Optimal cosmetic result for the implant in this patient
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition

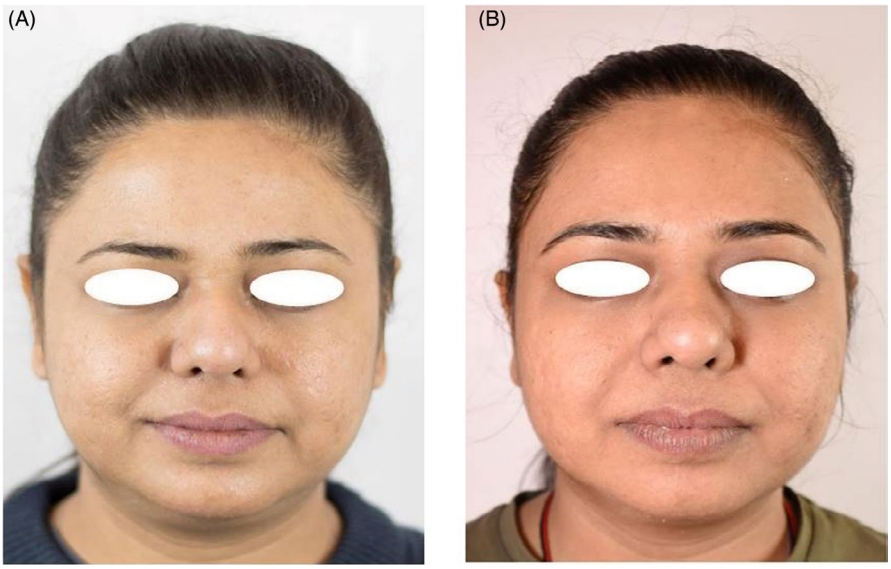

FIGURE 1 Clinical picture of patient 1. (A) Before treatment. (B) After 3 months of treatment

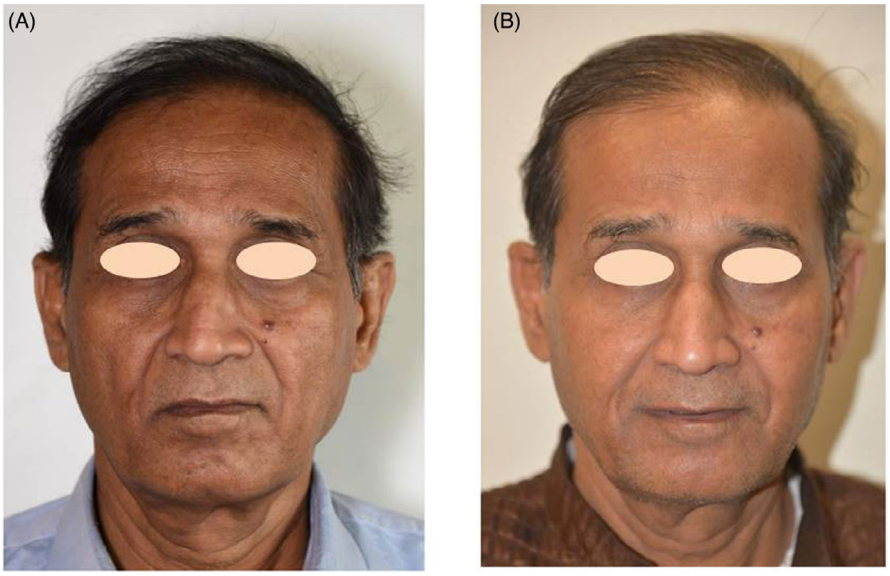

FIGURE 2 Clinical picture of patient 2. (A) Before treatment. (B) After 3 months of treatment

TABLE 4 Description of volume assessment scale, vermillion border assessment and lemperle rating scale

Volume Assessment	Vermillion Border Assessment	Lemperle Rating Scale
Very atrophic lips	Clearly defined	Just perceptible wrinkle
Less atrophic lips	Medium defined	Shallow wrinkle
Low atrophic lips	Not defined	Moderately deep wrinkle
		Deep wrinkle, Well-defined edges
		Very deep wrinkle redundant fold

improvements on both sides of the face, and one to two grades improvements at 3 months in WSRS score in 90% of the patients.

These results show a conversion of wrinkle lines from deep or moderately deep to shallow or hardly perceptible wrinkles. These changes sustained up to 6 months. (Figure 3) When we converted the score on a scale of 1–5, the mean score before treatment was 2.76, which reduced significantly to 2.14 after 3 months and 2.1 post 6 months of the treatment.

4.1.3 | Marionette line severity

Similarly, in Marionette line severity, there was major improvement seen in participants with reduction in deep and moderately deep wrinkles from 52.81% participants at baseline to 29.21% after

3 months. Thus, the majority of the participants showed significant improvements in Marionette line severity.

4.1.4 | The perioral and lip area

When evaluating the Lip Enhancement score, before treatment low volume, less volume, and very atrophic lips were found in 15.19%, 74.68%, and 5.06% participants, respectively. Post the treatment, these volume assessment scores were significantly ($p < 0.01$) changed to 26.58%, 67.09%, and 1.26% for low volume, less volume, and very atrophic lips, respectively. This clearly shows the shift with an improvement in volume, post-lip enhancement.

While evaluating vermilion border assessment, 27.85% and 45.56% participants were having clearly defined border, 69.62% and 4.37% participants with medium defined border and only 2.53% and 1.26% participants without defined border before treatment and after 3 months, respectively. These vermilion borders were found to be significantly changed ($p < 0.005$) in the assessment performed after 3 months of treatment. These results clearly indicated that more participants shifted from medium defined vermillion border lips to clearly defined vermillion border lips.

TABLE 5 Demographic distribution of patients according to age, gender, Fitzpatrick skin types, and BMI

Gender *N* (%)	Age range (years)	Fitzpatrick skin type	%	Age (mean years ± SD)	BMI (mean ± SD)
Male–34 (36.17%)	18–75	I	7.45	33.0 ± 1.3	24.80 ± 2.3
		II	12.77	39.7 ± 1.6	22.23 ± 1.7
		III	17.02	36.2 ± 1.3	25.69 ± 2.6
Female–60 (63.83%)		IV	48.94	37.7 ± 2.0	22.25 ± 1.5
		V	13.83	35.8 ± 2.7	24.1 ± 2.9
		VI	0	0	0

TABLE 6 Table depicting various areas of face treated with the particular volume of injection

Treated area	Injection volume/ml (Left side) Mean (Min-Max)	Injection volume/ml (Right side) Mean (Min-Max)	Injection volume total/ml Mean (Min-Max)
Glabellar lines	0.18 (0.1–0.2)	0.18 (0.1–0.2)	0.26 (0.2–0.4)
Nasolabial folds	0.92 (0.1–2.5)	0.90 (0.2–2.5)	1.78 (0.2–5)
Marionette lines	0.54 (0.1–1.5)	0.53 (0.05–1.5)	1.06 (0.2–3)
Lip augmentation	0.66 (0.25–1)	0.63 (0.1–1)	1.24 (0.1–2)
Lip contour	0.50 (0.25–1)	0.33 (0.1–1)	0.61 (0.1–2)

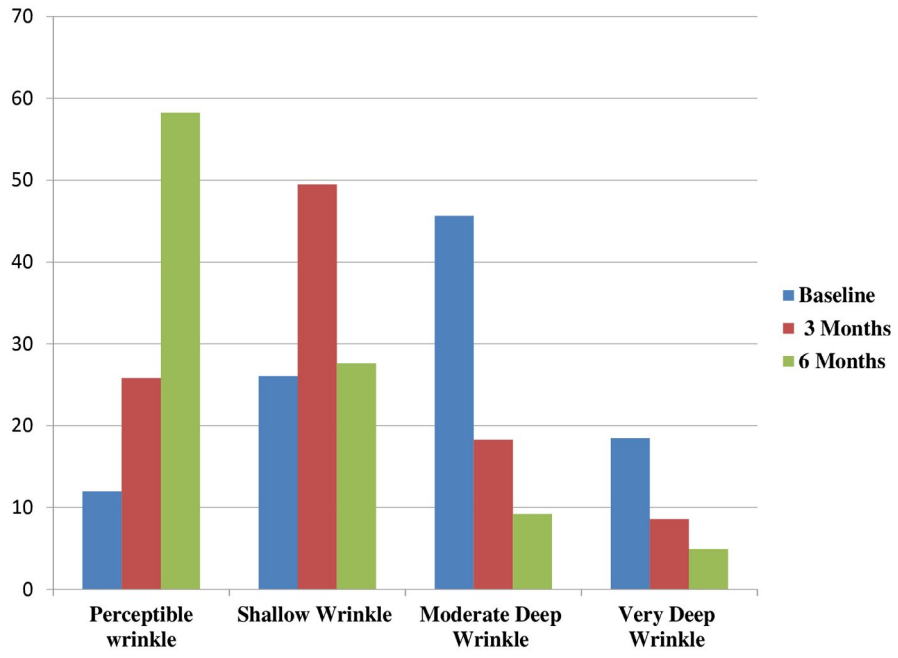

FIGURE 3 Image depicting results of the evaluation of nasolabial folds before treatment, after 3 months and 6 months of treatment

4.1.5 | Global esthetic assessment

Full Face Global Aesthetic Assessment conducted by GAIS was significantly improved in all participants except one. Overall, after 3 months of treatment, optimal cosmetic improvements were observed in 6.85% patients, marked improvement in 79.45%, obvious improvement observed in 12.33% patients, and no change observed in 1.37% patients. HA+L produced a better GAIS rating after baseline.

There was significant improvement seen from photographs in nasolabial folds and WSRS. Woman (Figure 1) and man (Figure 2) seen before treatment of HA+L in first figure and post 180 days of the treatment in the second figure.

4.2 | Safety

Only one SAE, unrelated to study, was reported. The patient suffered from pain and swelling due to fall at home resulting in wounded forehead and fractured right wrist. The SAE resolved after a while.

5 | DISCUSSION AND OVERALL CONCLUSION

Aging is a complex phenomenon that takes place over time. It is a distinctive and strongly self-reliant phenomenon that is both normal and controllable and can be tweaked using current cosmetic therapies.[15] Many treatment options have been tried since the past 100 years, starting from autologous fat to liquid paraffin, silicone oil, and bovine collagen. Due to these therapies, many complications have been reported such as hypersensitivity reactions and inflammatory reactions progressing to ulcerations, fistulas, and skin necrosis.[16]

Since 2003, when the global FDA's started approving hyaluronic acid products, many formulations have been approved for cosmetic usage, which have been recently popularized as injectable fillers.[17] This popularity can partially be attributed to its several advantages over the previously used similar products. In spite of general low immunogenic profile of hyaluronic acid, there have been a few reports of hypersensitivity or delayed allergic reactions.[18]

Hyaluronic acid fillers are used for "mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds."[19]

Topical anesthesia is commonly employed for comfort and pain minimization. Since the HA filler is pre-mixed with lidocaine, no separate pain management may be necessary.

The safety and efficacy of HA fillers have been compared with non-HA substances in various randomized controlled trials (RCTs). When compared to bovine collagen, HA filler is equally safe and provides durable effects for nasolabial fold correction.[20–22]

In our study also, the Wrinkle assessment scale for the nasolabial folds improved substantially and more number of participants were transferred to the shallow wrinkle group. Likewise, Marionette line severity was also significantly reduced. Overall, HA+L significantly improved both nasolabial fold and marionette line severity.

The treatment extended the earlier findings of non-controlled trials of efficacy and tolerability of HA for augmentation of soft facial tissue. This study also reported HA fillers to be equally effective, and tolerable in correcting the nasolabial folds.

Treatments with bovine collagen may require "touch-up" injections every four to six months.[23] According to the current study, at least for six months, a similar result can be produced with a smaller volume of HA+L.

This can be attributed to water re-absorption occurring from collagen suspension within 24 h after the injection.[24] Hyaluronic acid when stabilized, binds substantial amount of water molecules, which makes the cosmetic improvement more durable and long lasting.

Moreover, hyaluronic acid gel bears lower risk of allergic reactions in contrast to the bovine collagen.[24]

Significant improvements were also seen in lip enhancement score, which showed volume and the vermillion border to be significantly improved at 3 months of the study device injection.

During the study, safety and tolerability were evaluated, which showed that there was no adverse event reported, related to the study device. From this safety data, it can be concluded that the study device is safe for use.

Over-correction/under-correction, swelling, bruising/hematoma, redness/erythema, pruritus, migration, and visible bumps because of improper placements of excess injection are the most commonly noted initial symptoms. Type I and type III hypersensitive reactions are most common in animal-based products like bovine collagen.[25]

Evaluation for tolerability indicated similar local reactions for HA, as reported in earlier findings and post-marketing surveys. No hypersensitivity reactions were reported. Due to the syringes containing lidocaine, pain at the injection sites after the treatment was experienced only in very few cases. The local injection site reactions were generally low in frequency, intensity, and duration. It is also interesting to note a single case of hypersensitivity reaction following dermal filler in a patient post-COVID-19 episode. The accurate cause of delayed reaction post-dermal fillers with the COVID-19 anti-bodies is not understood completely.[26]

Ideally, as in the current treatment method using HA+L, the filler material in the injections should be biocompatible, easily injectable and have long-lasting effects. It should also be free of pain and other complications at the injection site.

HA+L (Jeunesso 24L) provided overall improvement in nasolabial folds and lip enhancement. Pre-mixed lidocaine provides a more comfortable injection experience in most individuals.

Due to its high tolerability and longevity, HA+L should be considered equivalent to the other standard and popular current injectable filler materials in the market.

CONFLICT OF INTERESTS

Nil.

ETHICS STATEMENT

This is Biotech Ophthalmics Pvt. Ltd. sponsoredPhase IV clinical trial for a product, having being granted approval from the respectivesite ethics committees.

AUTHOR'S CONTRIBUTION

Debraj Shome: Research project: Conception, Execution, Manuscript: Review and Critique. **Radha Atal Shah:** Manuscript: Review and Critique. **Dinesh Gowda:** Research project: Organization, Manuscript: Writing. **Sapna Vadera:** Research project: Organization, Manuscript: Writing. **Vaibhav Kumar:** Statistical analysis. **Manish Raj:** Statistical analysis. **Ali Atif:** Review and Critique. **Komal Doshi:** Research project: Organization, Manuscript: Writing. **Mrudul Vekaria:** Statistical analysis. **Meghna Pathak:** Review and Critique. **Rinky Kapoor:** Manuscript: Review and Critique.

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